



(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number:

0 304 802
A2

(12)

EUROPEAN PATENT APPLICATION

(21) Application number: 88113428.2

(51) Int. Cl.4: A61K 33/30, A61K 31/35,
A61K 31/44, // (A61K33/30,
31:44,31:35,31:19), (A61K31/44,
31:19), (A61K31/35,31:19)

(22) Date of filing: 18.08.88

(30) Priority: 25.08.87 US 89271

(71) Applicant: SPECTRAL BIOANALYSIS LTD.
12 York Gate
London NW1 4QS(GB)

(43) Date of publication of application:
01.03.89 Bulletin 89/09

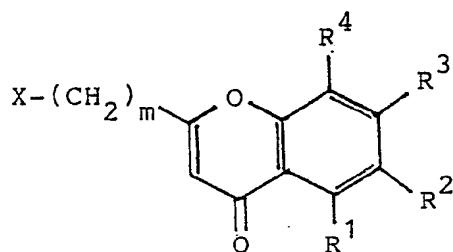
(72) Inventor: Kubler, Ulrich, Dr.
28 Knoebelstrasse
D-8000 Munich 22(DE)

(84) Designated Contracting States:
DE FR GB IT

(74) Representative: Hansen, Bernd, Dr.rer.nat. et
al
Hoffmann, Eitle & Partner Patentanwälte
Arabellastrasse 4 Postfach 81 04 20
D-8000 München 81(DE)

(54) Pharmaceutical composition and the use thereof.

(57) A pharmaceutical composition for topical administration comprising a pharmaceutically effective amount of a chromene derivative of formula I



wherein the radicals have the meaning given in claim 1 and bivalent zinc. The compositions are useful in the treatment of dermatoses, particularly atopic eczema and for cosmetic purposes.

EP 0 304 802 A2

PHARMACEUTICAL COMPOSITION AND THE USE THEREOF

FIELD OF THE INVENTION

5 The present invention relates to a pharmaceutical composition comprising a chromene derivative and bivalent zinc as well as the use of the said active ingredients for the making of medicaments effective against dermatoses and for cosmetic purposes.

10

BACKGROUND OF THE INVENTION

Since about 1965, chromene derivatives have been employed in the oral treatment of allergic asthma and rhinitis. The probably best known compound in this field is cromoglycinic acid. Since then structurally related chromene compounds have been synthesized and partly introduced in therapy of allergic disorders, such chromenes are e.g. minocromil, nedocromil, terbucromil, proxicromil, ambicromil, isocromil and others.

15 More recently, such chromenes have been used also in topical applications. So, sodium cromoglycate has been employed for the topical treatment of atopic eczema in children (Haider, S.A., British Medical Journal, i:1570 (1977)). However, sodium cromoglycate has also been found to be ineffective for topical treatment of atopic eczema in children (Thirumoorthy, T. et al, British Medical Journal, ii:500 (1978)).
 20 Topical treatment of atopic eczema with sodium cromoglycate has at best yielded only a statistically significant improvement of mild or moderately severe atopic eczema after nine weeks in actively treated patients (Ariyanayagam, M. et al, British Journal of Dermatology, 112:343 (1985)). Thus, previously known anti-eczema compositions for topical treatment of atopic eczema are not very effective for all degrees of atopic eczema, including severe atopic eczema and they are effective only after a prolonged period of treatment.

25 Although zinc oxide has been known to be an ingredient in ointments, pastes and powders, such has essentially been known for its effects as an astringent (The Merck Index, 8th Edition 1968). Zinc acetate has been found useful to influence favourably the effects of the macrolide antibiotic erythromycine in topical compositions for the treatment of acne (Zineryt - trademark of Roehm Pharma GmbH, Darmstadt). The application of such antibiotic substance is not always desirable subject to allergic reactions against the same, in cases of pregnancy etc..

35

OBJECT OF INVENTION

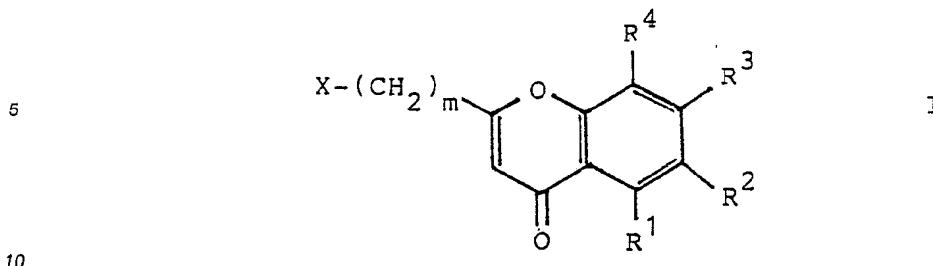
Accordingly, an object of the present invention is to provide an effective composition which is useful for the treatment of all degrees of dermatoses, including severe atopic eczema, and also for cosmetic purposes
 40 and which is effective after a short period of treatment. According to a further object of the invention the composition shall be free of antibiotics or hormone substances.

Other objects of the present invention will be apparent from the detailed description of the invention provided hereinafter.

45

SUMMARY OF INVENTION

The above-described objects of the present invention have been met by a composition comprising a pharmaceutically effective amount of bivalent zinc in combination with at least one chromene derivative of the general formula



where m, n, o, X, R¹ to R¹⁰ have the following meanings:

m an integer from 0 to 2

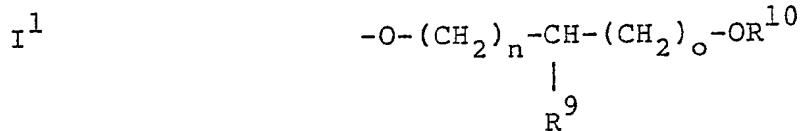
n an integer from 1 to 2

o an integer from 0 to 1

15 X is a carboxyl group or a phenyl radical which is optionally substituted by an alkyl group, having from 1 to 4 C atoms

R¹ is hydrogen, a hydroxyl group or an optionally substituted radical having the general formula

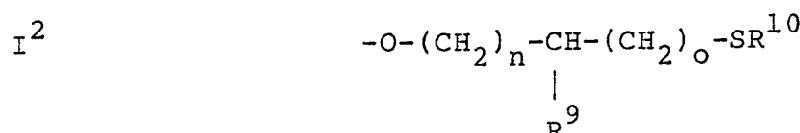
20



25

or

30



35 where m and n have the meaning above and R⁹ is a hydrogen atom, a hydroxyl group or an alkyl radical having from 1 to 4 C atoms,

R¹⁰ is a hydrogen atom, an alkyl radical with 1 to 4 C atoms or a phenyl radical which is optionally substituted 1 to 3 times by an alkyl radical, a hydroxyl group or an aliphatic radical or has the meaning of the general formula I, where R¹ to R⁴, m and X have the above named meaning,

40 R² is a hydrogen atom, a straight-chained or a branched alkyl radical with 1 to 4 C atoms or is a carboxyl group,

R³ is a hydrogen atom or an alkyl group having from 1 to 3 C atoms or it has the meaning of R¹,

or

R² and R³ together form a carbocyclic or heterocyclic ring of the general formulae Z, Z₁, Z₂ or Z₃, where

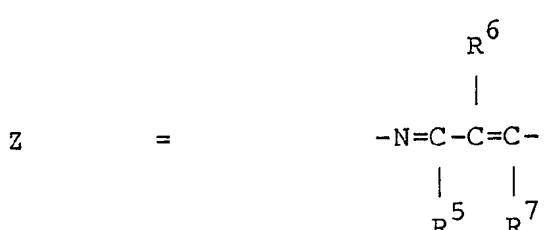
45 R⁵ has the meaning of a carboxyl group,

R⁶ is a hydrogen atom and

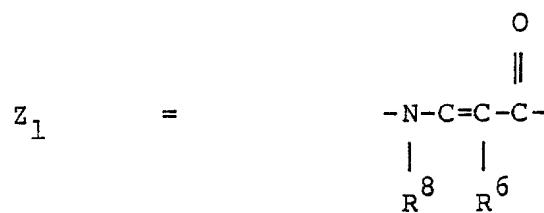
R⁷ is a hydrogen atom or an amino group which is optionally substituted by an alkyl radical having from 1 to 3 C atoms and

R⁸ is an alkyl group having from 1 to 3 C atoms:

50



5

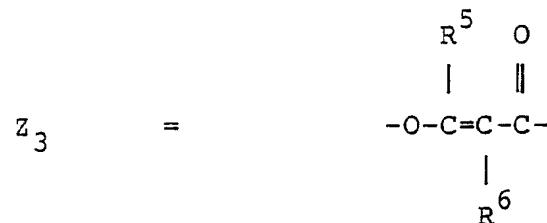


10

15



20



25

R^4 is a hydrogen atom or a straight-chained or branched alkyl radical having from 1 to 4 C atoms.

30

DETAILED DESCRIPTION OF THE INVENTION

The preferred compounds useful in the composition of this invention are shown in the table as below:

35

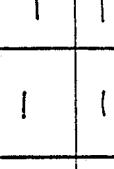
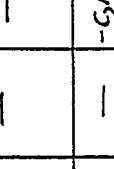
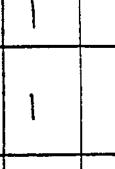
40

45

50

55

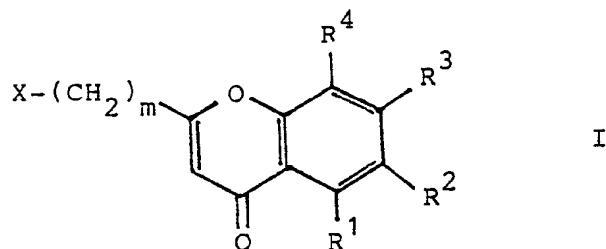
Table

active ingredient	<i>m</i>	<i>n</i>	<i>o</i>	<i>X</i>	<i>R</i> ¹	<i>R</i> ⁵	<i>R</i> ¹⁰	<i>R</i> ²	<i>R</i> ³	<i>R</i> ⁴	<i>R</i> ⁵	<i>R</i> ⁶	<i>R</i> ⁷	<i>R</i> ⁸	
chromo-glycinic acid	0	1	1	-COOH	$-\text{CH}_n-\text{CH}(\text{C}_6\text{H}_5)-\text{OR}^5-\text{OH}$		-H	-H	-H	-H	-	-	-	-	
anisochromic acid	0	-	-	-COOH	-H	-	-	$-\text{N}=\text{C}=\text{C}-$ $\text{R}^5 \text{ R}^6 \text{ R}^9$	$-\text{C}_3\text{H}_7$	$-\text{C}_3\text{H}_7$	-COOH	-H	-H	-	
FPL-52694	0	1	0	-COOH	$-\text{O}-(\text{C}_6\text{H}_5)-\text{CH}(\text{C}_6\text{H}_5)-\text{OR}^6-\text{C}_6\text{H}_5$	-H	-H	-H	$-\text{C}_3\text{H}_7$	-	-	-	-	-	
FPL-52757	0	-	-	-COOH	-OH	-	-	$-\text{CH}_2\text{C}_6\text{H}_5$	$-\text{CH}_2\text{C}_6\text{H}_5$	$-\text{CH}_2\text{C}_6\text{H}_5$	-	-	-	-	
FPL-55772	0	1	1	-COOH	-H	-OH		-H	$-\text{O}-(\text{C}_6\text{H}_5)-\text{CH}(\text{C}_6\text{H}_5)-\text{OR}^6$	$-\text{C}_3\text{H}_7$	-	-	-	-	-
neodochromic	0	-	-	-COOH	-H	-	-	$-\text{N}=\text{C}=\text{C}-$ $\text{R}^6 \text{ R}^5 \text{ R}^6$	$-\text{C}_3\text{H}_7$	-COOH	-H	-	-	-C ₄ H ₉	
terazucromic	0	-	-	-COOH	-H	-	-	$-\text{C}(\text{C}_6\text{H}_5)_3$	-H	$-\text{C}(\text{C}_6\text{H}_5)_3$	-	-	-	-	
phenacromic	0	-	-	-COOH	-OH	-	-	$-(\text{C}_6\text{H}_5)_4-$	$-\text{C}_3\text{H}_7$	-	-	-	-	-	
teracromic	0	1	1	-COOH	$-\text{O}-(\text{C}_6\text{H}_5)_n-\text{CH}(\text{C}_6\text{H}_5)-\text{S}-\text{R}^6-\text{OH}$	-C ₆ H ₅	-H	-H	$-\text{C}_3\text{H}_7$	-	-	-	-	-	
FPL-59257	1	2	0	-COOH	-	-H		-H	$-\text{O}-(\text{C}_6\text{H}_5)_n-\text{CH}(\text{C}_6\text{H}_5)-\text{OR}^6-\text{C}_6\text{H}_5$	-	-	-	-	-	
anisochromic	0	-	-	-COOH	-H	-	-	$-\text{O}-\text{C}=\text{C}-$ $\text{R}^5 \text{ R}^6 \text{ O}$	$-\text{C}_3\text{H}_7$	-COOH	-H	-	-	-	
isochromic	0	-	-	-COOH	-H	-	-	-COOH	-H	-H	-	-	-	-	-

Compounds being especially preferred in the present compositions are those of the general formula

5

10



15 wherein m = 0, n = 1, o = 0 or 1 and X is a carboxyl group, the other radicals having the meaning as shown hereinbefore.

16 The chromene derivative which is especially preferred in this invention is cromoglycinic acid and the pharmaceutically active salts, lower alkyl esters (C₁-C₁₀, particularly C₁-C₄) or amides which may be alkylated by C₁-C₄-alkyl thereof. Among the pharmaceutically preferred salts the alkali metal and alkaline earth metal salts can be mentioned. For some applications it may be possible to also use the zinc salts of 20 cromoglycinic acid and, in a broader aspect, of the respective chromene derivative.

21 The above chromene compounds are known as is the synthesis thereof so that no further discussion thereof is necessary.

22 The alkali metal when employed in the present invention is not critical thereto and can be any pharmaceutically acceptable alkali metal such as sodium, potassium, lithium, rubidium or combinations 25 thereof. Sodium is the preferred alkali metal.

26 The alkaline earth metal when employed in the present invention is not critical thereto and can be any pharmaceutically acceptable alkaline earth metal such as calcium or magnesium. Magnesium is the preferred alkaline earth metal.

27 The amount of the chromene derivative is in a pharmaceutically or cosmetically effective amount which 30 in general is from about 1% to about 25%, preferably from about 2% to about 10% by weight based on the total weight of the composition.

31 The specific bivalent zinc employed in the present invention is not critical thereto and can be in the 35 form of bivalent zinc compounds such as zinc oxide, zinc lactate, zinc chloride, zinc carbonate, zinc sulfate, zinc acetate or combinations thereof. Zinc oxide is the preferred form of bivalent zinc employed in the present invention because it has a white colour and easily masks the skin well. If the particular form of bivalent zinc employed is highly acidic, pharmaceutically acceptable buffering agents can also be employed to adjust the pH to about physiological levels, i.e. about pH 5.0 to 7.7.

36 The bivalent zinc is also employed in an effective amount ranging from about 1% to 25%, preferably 40 from about 4% to about 10% by weight of bivalent zinc compound based on the total weight of the composition.

37 The composition of this invention is highly effective in the treatment of skin disorders at mammals (cats, 45 horses, dogs) and particularly man at any degree. Normally the composition will be applied as a pharmaceutical but also cosmetic applications may be possible. The skin disorders which can be successfully treated are dermatoses and these comprise particularly eczema including atopic eczema, psoriasis, dermatitic disorders due to allergic reaction (e.g. antibiotic, metals like Ni, organic chemicals), 50 ulcers including colitis ulcerosa, urticaria, inflammatory skin conditions, e.g. due to Crohn's disease and others. The cosmetic applications may have to do with treatment of acne, of wrinkles and of sun burns etc..

51 The compositions of this invention are normally applied in topical administration. Such topical applications can be in form of solution, emulsion, suspension, ointment, cream, gel, lotion or spray. The use of 55 emulsions, gels and ointments is generally preferred.

56 The making of such topical compositions is known to the skilled in the art. Some typical examples are given though hereinafter:

55

1. emulsion

oil phase

10 g cetylstearyl alcohol
 10 g cetylstearyl sulfonate
 5 10 g olive oil
 5 g wool wax
 10 g zinc oxide

10 water phase

100 ml double distilled water
 4 g chromene compound

15

2. ointment

5 g zinc acetate-dihydrate
 5 g chromene compound
 20 25 g paraffine oil
 60 g paraffine wax
 5 g wool fat

25 3. lotion

6 g chromene compound
 3 g zinc diacetate dihydrate
 60 g ethanol (95%)
 30 20 g di-isopropyl sebacate
 10.5 g distilled water
 0.5 g EDTA

35 4. cream

8 g chromene compound
 5 g wool alcohol
 25 g solid paraffine mixture
 40 35 g liquid paraffine
 7 g zinc lactate
 20 g purified water

The topical compositions can be made using known techniques in the art for the making of such compositions. While topical composition of varying nature as above can be utilized, often the use of an oil-in-water or water-in-oil emulsion are preferred.

For the making of oil based emulsions the oil of the oil phase can be any pharmaceutically acceptable oil such as a vegetable oil, e.g. olive oil, soybean oil, jojoba oil, coconut oil, avocado oil, etc., an animal oil such as whale oil and mink oil, etc., or combinations thereof. Olive oil is the preferred oil because it is non-allergenic.

50 The water of the water phase may be any pharmaceutically acceptable water such as sterile water, deionized water, double distilled water or tap water. Double distilled water is the preferred water because of the high degree of purity thereof.

55 If desired, additives such as preservatives, emulsifiers, emollients, biologically active substances such as naturally occurring flavonoides, sun screens, colorants, fragrances or other additives typically employed in topical compositions can be added to the composition of the present invention.

Examples of preservatives which can be employed include para-benzoic acid, sorbic acid and tocopherols. Para-benzoic acid can be added in an amount of from about 0.5 to 3%, preferably from about 1% to about 1.5% by weight based on the total weight of the composition. Sorbic acid can be added in an

amount of from about 0.05 to 0.1% by weight based on the total weight of the composition. Tocopherols can be added in an amount of from about 0.1 to 0.2% by weight based on the total weight of the composition. Generally, the preservatives are added to the water phase. For solutions, sprays and lotions the use of pharmaceutically acceptable chelates and particularly EDTA has been found useful for additional 5 stabilization.

Examples of emulsifiers which can be employed in the present invention include cetylstearyl alcohol, cetylstearyl sulfonate, eucerin, Eucerit, Emulgol (L. Givaudan & Co.), Emulgators 8077 and 8092 (Dragoco GmbH) and Emulgator oil/water (Ciba Geigy) or combinations thereof. Additional examples of emulsifiers which can be employed in the present invention are described in Kirk-Othmer Encyclopaedia of Chemical 10 Technology 3rd Ed. (John Wiley & Sons, 1979, Vol. 7, pages 146-148), which is incorporated by reference herein. The emulsifiers can be added in an amount of from about 10% to 20%, preferably from about 12% to 15% by weight based on the total weight of the composition. Generally, the emulsifiers are added to the oil phase.

Examples of the emollients which can be employed in the present invention include wool wax, lecithin, 15 cholesterin, eucerin, Eucerit and neatfoot oil or combinations thereof. The emollients can be added in an amount of from about 1.0% to 10%, preferably from about 3.0% to 5.0% by weight based on the total weight of the composition. Generally, the emollients are added to the oil phase.

Examples of sun screens which can be employed in the present invention include triethanolamin, benzylanthranilate and 2-hydroxy-4'-methoxybenzophenone or combinations thereof. Additional examples of 20 sun screens which can be employed in the present invention are described in Kirk-Othmer Encyclopaedia of Chemical Technology 3rd Ed. (John Wiley & Sons, 1979, Vol. 7, pages 152-154), which is incorporated by reference herein. The sun screens can be added in an amount of from about 0.5% to about 6.0%, preferably from about 1.0% to 5.0% by weight based on the total weight of the composition. Generally, the sun screens are added to the oil phase.

Colorants and fragrances as well as other additives can easily be added to the composition of the 25 present invention in amounts conventionally employed as described in e.g. Kirk-Othmer Encyclopaedia of Chemical Technology 3rd Ed. (John Wiley & Sons, 1979, Vol. 7, pages 143-176), which is incorporated by reference herein.

Emulsions of the present invention can be produced by first preparing an oil phase containing a water-insoluble bivalent zinc compound, such as zinc oxide, and then preparing an aqueous phase containing the 30 chromene derivative, e.g. an alkali metal or alkaline earth metal cromoglycate. Bivalent zinc oxide can also be added to the water phase instead of the oil phase if desired. When the form of bivalent zinc is a water-soluble bivalent zinc compound, such as zinc chloride, it is added generally to the water phase. The oil phase is then mixed with the water phase to achieve an oil-in-water emulsion or the water phase is added to 35 the oil phase to achieve a water-in-oil emulsion.

The oil-in-water and water-in-oil emulsions can be prepared using conventional emulsification techniques such as a homogenizer, an emulsion mill and rollers. The particular size of the emulsion formed is not critical as long as the particle size is sufficient for the emulsion to be stable over a period of time.

The temperature for preparing the oil phase will be above the melting point of the oil but not above the 40 temperature at which the chromene compound and additives are degraded. Generally, the temperature is about 40 °C to about 75 °C.

The composition of this invention is generally applied to the skin in an amount of about 0.005 g to about 45 0.03 g per square centimeter of skin, preferably about 0.01 g to about 0.02 g per square centimeter of skin, although more or less can be employed as required by the patient's condition and the therapy desired.

The following example is provided for illustrative purposes only and is in no way intended to limit to 50 scope of the present invention. Unless otherwise indicated herein, all parts, percents, ratios and the like are by weight.

55 Example

An oil phase containing the following components was prepared by admixing these components and melting such at 75 °C. Thereafter, the water phase containing the following components was prepared by admixing these components at 40 °C. Next, the oil phase was mixed with the water phase to prepare an oil-in-water emulsion.

oil phase

10 g cetylstearyl alcohol
 10 g cetylstearyl sulfonate
 5 10 g olive oil
 5g wool wax
 10g zinc oxide

10 water phase

100 ml double distilled water
 4 g sodium cromoglycate
 The resulting emulsion was employed to treat 14 adults ranging from 20-60 years of age (12 females
 15 and 5 males) and 3 children ranging from the age of 9-12 years (2 females and 1 male).

At the start of the trial, the atopic eczema of each patient was assessed clinically into three groups (mild = I, moderately severe = II, severe = III) by recording the symptoms of itching, erythema, macules, lichenification, vesiculation, dryness and excoriation. The total severity was calculated by the addition of the score of each measurement over four main areas of eczema on the patients. During this trial, the patients
 20 did not receive any external medication, corticoids or antihistamines other than the use of the composition of the present invention.

The composition of the present invention was topically administered twice a day (in the morning and in the evening) in an amount of about 0.015 g per square centimeter. During the trial, one patient was excluded because the patient began taking corticoids (a member of group II) and another patient withdrew
 25 from the study because of dryness of the skin caused by application of the composition of the present invention (a member of group II).

During the study, the patients recorded the day when they were free of itching, vesiculation and pruritus and were evaluated every two days for the degree of severity of eczema. From the 15 patients which finished the study, 7 were in group I and 8 were in group II at the time of first clinical assessment. Two of
 30 the 7 of group I were free of symptoms at the third day of administering the composition of the present invention. Of the other 13 patients, they were free of symptoms at the seventh day (8 patients) or the tenth day (5 patients). Of the 15 successfully treated patients, 4 needed no additional medication for weeks, 6 others administered the composition of the present invention occasionally to avoid excessive exacerbation and 5 administered the composition of the present invention routinely every day.

35 In previous trials of topical application of sodium cromoglycate alone employing proportionately the same amount of cromoglycate, a statistically significant improvement was not reached until 9 weeks after administration whereas using the composition of the present invention, improvement was observed after an average of only 7-10 days. Thus, the composition of the present invention is advantageous in that, due to the interaction of the alkali metal or alkaline earth metal cromoglycate and the bivalent zinc, it is effective in
 40 a shorter period of time than previous compositions employed for the treatment of atopic eczema and containing alkali metal or alkaline earth metal cromoglycate alone.

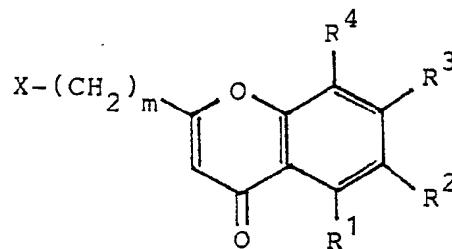
similar results are obtainable when replacing the cromoglycate by the chromene compounds as disclosed hereinbefore.

45 The invention has been described with reference to specific embodiments thereof. However, it will be apparent to one skilled in the art that various changes and modifications can be made therein without departing from the spirit and scope thereof.

Claims

50 1. Pharmaceutical composition comprising a pharmaceutically effective amount of bivalent zinc in combination with at least one chromene derivative of the general formula

5



I

10

where m, n, o, X, R¹ to R¹⁰ have the following meanings:

m an integer from 0 to 2

n an integer from 1 to 2

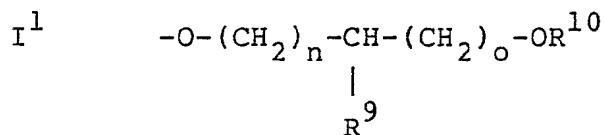
o an integer from 0 to 1

15 X is a carboxyl group or a phenyl radical which is optionally substituted by an alkyl group, having from 1 to 4 C atoms

R¹ is hydrogen, a hydroxyl group or an optionally substituted radical having the general formula

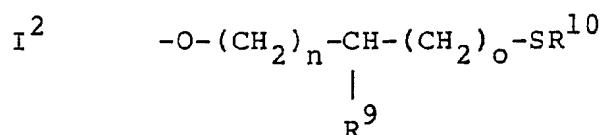
20

25



or

30



35

where m and n have the meaning above and R⁹ is a hydrogen atom, a hydroxyl group or an alkyl radical having from 1 to 4 C atoms.

40 R¹⁰ is a hydrogen atom, an alkyl radical with 1 to 4 C atoms or a phenyl radical which is optionally substituted 1 to 3 times by an alkyl radical, a hydroxyl group or an aliphatic radical or has the meaning of the general formula I, where R¹ to R⁴, m and X have the above named meaning,

R² is a hydrogen atom, a straight-chained or a branched alkyl radical with 1 to 4 C atoms or is a carboxyl group,

45 R³ is a hydrogen atom or an alkyl group having from 1 to 3 C atoms or it has the meaning of R¹, or

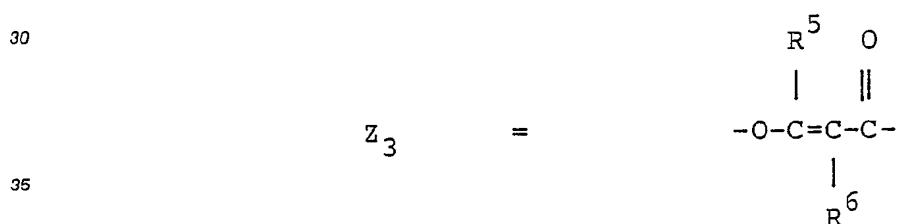
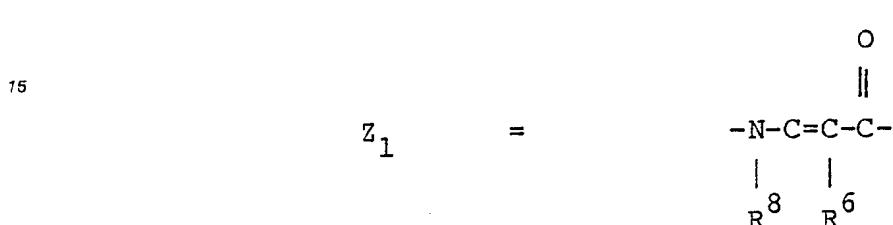
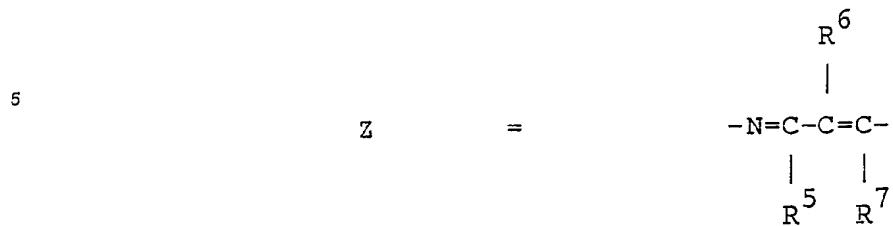
R² and R³ together form a carbocyclic or heterocyclic ring of the general formulae Z, Z₁, Z₂ or Z₃, where R⁵ has the meaning of a carboxyl group,

R⁶ is a hydrogen atom and

50 R⁷ is a hydrogen atom or an amino group which is optionally substituted by an alkyl radical having from 1 to 3 C atoms and

R⁸ is an alkyl group having from 1 to 3 C atoms:

55



40 R⁴ is a hydrogen atom or a straight-chained or branched alkyl radical having from 1 to 4 C atoms.

2. Composition according to claim 1, characterized in that the chromene derivative is a compound of formula I wherein m = 0, n = 1, o = 0 or 1, and X is a carboxyl group and the other radicals have the meaning shown in claim 1.

45 3. Composition according to claims 1 or 2, characterized in that the chromene derivative is cromoglycinic acid or a pharmaceutically acceptable salt thereof.

4. Composition according to any of the preceding claims in that it is in form appropriate for topical administration.

50 5. Composition according to any of the preceding claims, characterized in that said bivalent zinc is in the form selected from the group consisting of zinc oxide, zinc lactate, zinc chloride, zinc carbonate, zinc sulfate, zinc acetate or combinations thereof.

6. Composition according to any of the preceding claims, wherein said chromene derivative is present in an amount from about 1% to about 25% by weight based on the total weight of the composition.

55 7. Composition according to any of the preceding claims, wherein said bivalent zinc is present in an amount of from about 1% to 25% by weight of bivalent zinc compound based on the total weight of the composition.

8. Topical composition according to any of the preceding claims containing cromoglycinic acid or a salt thereof and bivalent zinc in form of an aqueous emulsion, suspension, ointment, cream, lotion or spray.

55 9. The use of a chromene derivative in combination with bivalent zinc according to any of the preceding claims for the making of a medicament effective against dermatoses, particularly atopic eczema.

10. The use of a chromene derivative in combination with bivalent zinc according to any of the preceding claims for cosmetic treatment of skin of mammals, notably man.

5

10

15

20

25

30

35

40

45

50

55